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Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
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(54) Title: CAROTENOID COMPOSITION AND METHOD FOR PROTECTING SKIN

(57) Abstract: A method for protecting skin against damages caused by ultra-violet (uv) radiation from the sun, comprising administering to a subject in need of protection an effective amount of a composition containing lycopene from a natural source and one or more carotenoid selected from among phytoene and phytofluene or mixtures thereof.

Carotenoid Composition and Method for Protecting Skin

Field of the Invention

The present invention relates to the field of protection from sun radiation, particularly to methods and compositions effective in protecting skin.

Background of the Invention

It is well established that prolonged exposure to sun has damaging effects on the skin. Particularly, the uv radiation from the sun is known to cause erythema of the skin, sunburn and skin cancer. Protection of the skin from uv radiation can be achieved by protective attire as well as by protection in the form of topical compositions of various protective ingredients. A particular group of protective compositions are intended for oral administration. Oral compositions contain active ingredients which are delivered to the skin via an internal transport mechanism and thus protect the skin from uv radiation damage. A particular group of active ingredients which are suitable for use with said oral compositions are carotenoids. U.S. patent 3,920,834 describes the use of a mixture of carotenoids wherein cathaxanthin is the primary carotenoid in the composition. However, the use of cathaxanthin is known to be limited due to adverse effects it may have on pigmentation. U.S. patent 5,290,605 describes food-stuff and beverages intended for providing protection to the skin against uv sun radiation. Said foodstuff and beverages comprising carotenoids as well as ascorbic acid, tocopherols, coenzyme Q10 and reduced glutathione. U.S. patent 6,110,478 further describes a composition for protecting skin against uv radiation and the harmful effects thereof, wherein the composition contains a pro-vitamin A carotenoid and lycopene. The use of such a composition is limited by the negative effect pro-vitamin A carotenoids may have on the subject's health at certain dosage levels. An excess of vitamin A, which is produced in the body from pro-vitamin A carotenoids, was found to have adverse effects on health. Stahl *et al* ("Dietary Tomato Paste Protects against Ultraviolet Light-induced Erythema in Humans", *Biochemical and Molecular Action of Nutrients, Research Communication*, (2001) 1449-1451) have shown the protective effect of tomato paste which is known to contain *inter alia* lycopene, β-carotene and tocopherol, against uv light-induced erythema. However, Stahl has reported

a problem in achieving desired carotenoid serum levels, suggesting poor bioavailability.

Accordingly, there is a long felt need to develop a composition for protecting skin against uv radiation which is suitable for oral administration and is safe at a wide range of dosages.

It is therefore a purpose of the present invention to provide a method for protecting skin against damages caused by ultra-violet (uv) radiation from the sun.

A further purpose of the present invention is to provide a carotenoid composition effective in protecting the skin against the damages of uv radiation and which does present potential health risks.

It is yet another purpose of the present invention to provide a method and composition that overcome the disadvantages of the known art.

Other objectives of the invention will become apparent as the description proceeds.

Summary of the Invention

The present invention provides a method for protecting skin against damages caused by ultra-violet (uv) radiation from the sun, comprising administering to a subject in need of protection an effective amount of a composition containing lycopene from a natural source and one or more carotenoid selected from among a group consisting of phytoene and phytofluene. Optionally, said composition may further contain vitamin E.

Further provided by the present invention is a composition comprising of 6% to 25% lycopene of a natural source and more than 0.3% of one or more carotenoid selected from among a group consisting of phytoene and phytofluene. Optionally, said composition may contain 1% to 4% vitamin E.

Further provided by the present invention is the use of a carotenoid composition containing lycopene from a natural source and one or more carotenoid selected from among a group consisting of phytoene and phytofluene as a protective agent against uv light-induced damage to skin. Optionally, said composition may further contain vitamin E.

The present invention further provides administration forms for the presently claimed composition, wherein said administration form may be a food-stuff, beverage or pharmaceutically acceptable dosage form.

Description of the Drawings

Fig. I – Comparison of protection of various carotenoid compositions against erythema (see Example 2 for clarifications of terms appearing in graph)

Detailed Description of a Preferred Embodiment of the Invention

The following description is illustrative of embodiments of the invention. The following description is not to be construed as limiting, it being understood that the skilled person may carry out many obvious variations to the invention.

Throughout the description, percentages of components are by weight, unless specifically noted differently. The terms "lycopene of natural sources" and "natural lycopene" are synonymous throughout the application and refer to lycopene from vegetables, fruits, plant matter, fungus and fungal sources, and natural bio-mass.

It has surprisingly been found that carotenoid compositions which contain natural lycopene and one or more carotenoid selected from among a group consisting of phytoene and phytofluene, are effective in protecting skin against damages caused by uv radiation from the sun, wherein said damages are erythema and sunburn. Furthermore, unexpectedly, it has been found in the present invention that natural lycopene is significantly more effective in protecting skin against uv radiation damages than synthetic lycopene. A further surprising finding according to the present invention, is that the

addition of phytoene and/or phytofluene to the natural lycopene composition improves the effectiveness of the composition in protecting skin against uv radiation damage.

According to an embodiment of the method of the present invention, 1 mg to 10 mg of a composition comprising 6% to 15% of natural lycopene and 0.3% to 1.5% of one or more carotenoid selected from among phytoene and phytofluene are administered to a subject. Preferably, about 5 mg of a composition comprising 6% of natural lycopene, 0.5% phytoene and 0.5% phytofluene are administered.

In yet a further embodiment of the present method the aforementioned compositions may contain 1.5% to 2.5% of vitamin E. preferably, said composition containing about 6% natural lycopene, 0.5% phytoene, 0.5% phytofluene and 2% vitamin E.

According to a particular embodiment of the invention, the compositions employed comprise natural lycopene and one or more additional carotenoid selected from among phytoene and phytofluene wherein the ratio between the lycopene and additional carotenoids is in the range of 20:1 to 5:1, preferably 8:1 to 5:1.

The indicated dosages refer to a healthy adult in the weight range of 50 Kg to 70 Kg and thus may vary according to body size. However, preferably, the dosage is adjusted so that the carotenoid serum level of the subject reaches a level within the range of 0.3 to 1.2 μM (micromole/liter), wherein serum levels of lycopene are 0.2 to 0.6 μM, phytoene 0.08 to 0.2 μM and phytofluene 0.08 to 0.4 μM. Dosages of total carotenoids may be daily in single or multiple doses, of about 2 to 15 mg/day, preferably 5 mg/day.

The compositions are administered by means known in the art, which will achieve the desired carotenoid serum levels. Oral administration is preferred. The oral administration can be in the form of a capsule, gel-cap, pellet, soft gel capsule or tablet which contain the carotenoid compositions. Said oral dosage forms may contain pharmaceutically acceptable excipients, additives, carriers and stabilizers. Particularly important additives are of the type which improve bioavailability of the carotenoids, e.g. oils and surfactants.

Said oral dosage forms are prepared according to conventional methods known from the art. A preferred means of oral administration is via foodstuff and beverages. Thus, the carotenoid composition is added to foodstuff or beverages. The amount of carotenoid composition in the foodstuff and beverage is adjusted to meet the above-mentioned dosages.

According to a particular embodiment of the present method, administration of the composition is preferably started before exposure to uv radiation. Preferably, 7 to 30 days before exposure, and administration is continued during exposure.

According to a further aspect of the present invention there is provided a novel carotenoid composition comprising of 6% to 15% lycopene of a natural source and 0.3% to 1.5% of one or more carotenoid selected from among a group consisting of phytoene and phytofluene. Preferably, the composition comprises 6% of natural lycopene, 0.5% phytoene and 0.5% phytofluene.

According to yet a further embodiment the composition may further comprise of 1.5% to 2.5% vitamin E. Preferably the composition contains 6% natural lycopene, 0.5% phytoene, 0.5% phytofluene and 2% vitamin E.

The compositions of the present invention comprise natural lycopene and one or more additional carotenoid selected from among a group consisting of phytoene and phytofluene wherein the ratio between the lycopene and additional carotenoid is in the range of 20:1 to 5:1, preferably 8:1 to 5:1. Optionally, the composition may further contain vitamin E wherein the ratio between the lycopene and the vitamin E is in the range of 10:1 to 2:1, preferably 8:1 to 3:1.

A particular embodiment of the present invention relates to solid and liquid oral dosage forms selected from among a group comprising of a capsule, gel-cap, pellet, soft gel capsule, tablet, or other liquid or solid oral dosage forms known in the art, which comprises a carotenoid composition which contains 5 mg to 15 mg of natural lycopene

and 0.5 mg to 3.5 mg of one or more additional carotenoid selected from among phytoene and/or phytofluene. Said oral dosage form may further comprise 1.5 mg to 8 mg of vitamin E. Preferably, said oral dosage form comprises 5 mg of natural lycopene, 0.5 mg phytoene, 0.45 mg phytofluene and 1.8 mg of vitamin E. Said dosage form may further contain a pharmaceutically acceptable adjuvant, excepient, carrier, filler, stabilizer or additive.

The present invention further relates to foodstuff or beverages which contains a carotenoid composition as described herein. The foodstuff or beverage contain 5 mg to 15 mg of natural lycopene and 0.5 mg to 3.5 mg of one or more carotenoid selected from among a group consisting of phytoene and phytofluene. Said food-stuff or beverage may further contain 1.5 mg to 8 mg of vitamin E. Preferably, said food-stuff or beverage comprises 4.1 mg of natural lycopene, 2.2 mg phytoene, 1.6 mg phytofluene and 3.8 mg of vitamin E.

The present invention presents the following advantages:

1. The compositions do not contain pro-vitamin A carotenoids, which at certain elevated dosages may be a health hazard. Thus, the present invention is safer and does not have the health risks as compositions described in the prior art.
2. The protection is provided via in-vivo activity. Thus, the protective composition cannot be washed away or depleted like topical protective compositions.
3. The compositions of the present invention have been shown to have improved bioavailability compared to other sources of natural lycopene and in comparison to synthetic lycopene, and thus offer improved protection against uv light-induced skin damage.
4. The composition may bring about tanning of the skin to a brown hue in subjects exposed to uv radiation without the damages associated with uv radiation. This has both health and aesthetic advantages.

Examples

Example 1: Preparation of Carotenoid Composition

The lycopene used throughout the Examples is natural lycopene by LycoRed®.

Formulation 1: each capsule contains:

Lycopene 4.88 mg

Phytoene 0.48 mg

Phytofluene 0.44 mg

Vitamin E 1.81 mg

in soft gel capsules which are prepared according to standard procedures known to the skilled artisan.

Formulation II: each soft drink bottle contains

Lycopene 4.1 mg

Phytoene 2.2 mg

Phytofluene 1.6 mg

Vitamin E 3.8 mg

Formulation III

Lycopene 5.5 mg

Vitamin E 2.0 mg

Example 2: Comparative Example of Protection against erythema

Three treatment groups consumed the following lycopene supplements for 12 weeks:

a) Group 1 – Lyc-O-Mato® soft gel capsules[1)] (1 capsule twice a day)

b) Group 2 – Lyc-O-Guard™ drink[2)] (250 ml bottle twice a day)

c) Group 3 – Synthetic lycopene hard shell capsules[3)] (1 capsule twice a day)

1) The carotenoid fraction is a tomato extract containing natural lycopene, phytoene, phytofluene and tocopherols. 2) The carotenoid fraction is a tomato extract similar to Lyc-O-Mato® which is further enriched with phytoene, phytofluene and tocopherols. 3) The carotenoid fraction contains synthetic lycopene and tocopherols.

The minimal erythema dose (MED), which is the minimal dose of uv radiation which produces a minimal erythema (reddening of the skin) after 24 hours was determined by exposing different small areas of skin to increasing doses of uv radiation. The testing of the effectiveness of the carotenoid supplementation was tested by exposing the subjects to 1.25 of the individual MED at 0, 4 and 12 weeks from the beginning of lycopene supplementation. The effect of the radiation on the reddening and pigmentation of the skin was measured by a Minolta chronometer. The "a" and "b" value of the chronometer correlate to the reddening and pigmentation of the skin, respectively. The erythema (reddening) was determined 24 hours after radiation of uv radiation, by subtracting the value of "a" before radiation from the value of "a" 24 hours after radiation. The value obtained is denoted by "Δa". Larger values of Δa correlate with increased erythema of the skin. Fig. 1 clearly demonstrates the improved protective effect against uv induced erythema, Lyc-O-Mato and Lyc-O-Guard have over synthetic lycopene.

While embodiments of the invention have been described by way of illustration, it will be apparent that the invention may be carried out with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

CLAIMS

1. A method for protecting skin against damages caused by ultra-violet (uv) radiation from the sun, comprising administering to a subject in need of protection an effective amount of a composition containing lycopene from a natural source and one or more carotenoid selected from among phytoene and phytofluene or mixtures thereof.

2. A method according to claim 1 wherein said composition further contains vitamin E.

3. A method according to claim 1, wherein 1 mg to 10 mg of a carotenoid composition comprising of 6% to 15% lycopene of a natural source and 0.3% to 1.5% of one or more carotenoid selected from among phytoene and phytofluene or mixtures thereof are administered.

4. A method according to claim 3 wherein said composition contains 1.5% to 2.5% vitamin E.

5. A method according to claim 3, wherein about 5 mg are administered.

6. A method according to claim 4, wherein about 5 mg are administered.

7. A method according to any of claims 1 to 6 wherein the carotenoid serum level of the subject reaches a level within the range of 0.3 to 1.5 μM.

8. A method according to claim 8 wherein carotenoid serum levels of the subject reaches a level of about 1.2 μM.

9. A method according to any one of claims 1 to 8 wherein administration is in the form of a capsule, gel-cap, pellet, soft gel capsule or tablet which contain the carotenoid compositions.

10. A method according to any one of claims 1 to 8 wherein administration is in the form of oral administration via foodstuff or beverages.

11. A method according to any one of claims 1 to 11 wherein administration begins 7 to 30 days before exposure to uv radiation.

12. A carotenoid composition comprising of 6% to 15% lycopene of a natural source and 0.3% to 1.5% of one or more carotenoid selected from among phytoene and phytofluene or mixtures thereof.

13. A composition according to claim 12 further containing 1.5% to 2.5% vitamin E.

14. A composition according to claim 12 which contains about 6% natural lycopene, 0.5% phytoene and 0.5% phytofluene.

15. A composition according to claim 13 which contains about 6% natural lycopene, 0.5% phytoene, 0.5% phytofluene and 2% vitamin E.

16. An oral dosage form comprising of 5 mg to 15 mg of natural lycopene and 0.5 mg to 3.5 mg of one or more carotenoid selected from among phytoene and/or phytofluene or mixtures thereof.

17. An oral dosage form according to claim 16 further comprising 1.5 mg to 8 mg of vitamin E.

18. An oral dosage form according to claim 17 comprising 5 mg of natural lycopene, 0.5 mg phytoene, 0.45 mg phytofluene and 1.8 mg of vitamin E.

19. An oral dosage form according to claim 16 further containing a pharmaceutically acceptable adjuvant, excepient, carrier, filler, stabilizer or additive.

20. Use of a composition as described in any of claims 12 to 15 in the preparation of a skin protecting composition.

21. Use of a composition as described in any of claims 12 to 15 as a skin-protecting agent.

22. A composition according to any of claims 12 to 15 for use in the protection of skin against damages caused by uv radiation.

23. Foodstuff and beverage containing a composition as described in any of claims 12 to 15.

24. Foodstuff or beverage comprising of 5 mg to 15 mg of natural lycopene and 0.5 mg to 3.5 mg of one or more carotenoid selected from among a group consisting of phytoene and phytofluene.

25. Foodstuff or beverage according to claim 24 further comprising 1.5 mg to 8 mg of vitamin E.

26. Foodstuff or beverage according to claim 25 comprising 4.1 mg of natural lycopene, 2.2 mg phytoene, 1.6 mg phytofluene and 3.8 mg of vitamin E.

27. A pharmaceutically acceptable oral dosage form containing a composition as described in any of claims 12 to 15.

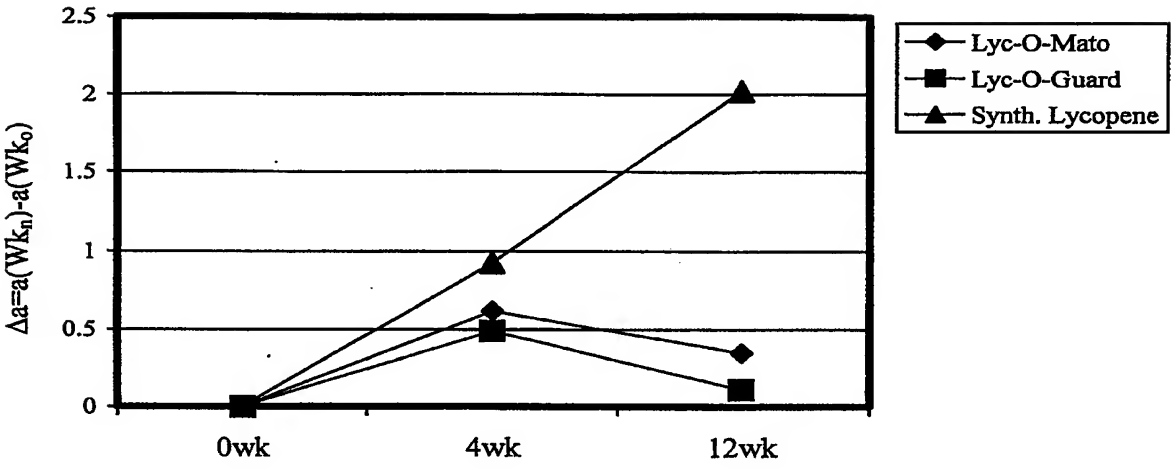
2.5
2
1.5
1
0.5
0
Δa=a(Wk$_n$)-a(Wk$_0$)
0wk
4wk
12wk
Lyc-O-Mato
Lyc-O-Guard
Synth. Lycopene

Fig. 1

INTERNATIONAL SEARCH REPORT

Internati — Application No
PCT/IT 02/00875

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/42 A61K31/01 A23L1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	O. KUCUK ET AL.: "Phase II Randomized Clinical Trial of Lycopene Supplementation before Radical Prostatectomy" CANCER EPIDEMOLOGY, BIOMARKERS PREVENTION, vol. 10, August 2001 (2001-08), pages 861-868, XP002233572 page 863, left-hand column, paragraph 2 page 865, left-hand column, last paragraph -/--	12-19, 22-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2003	17/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boeker, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IL 02/00875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	I. PAETAU ET AL.: "Chronic ingestion of lycopene-rich tomato juice or lycopene supplements significantly increases plasma concentratios of lycopene and related tomato carotenoids in humans" AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 68, 1998, pages 1187-1195, XP002233573 page 1188, left-hand column, last paragraph; table 1 ---	12-19, 22-27
T	ABOUT LYC-O-MATO TM, 'Online! XP002233574 Retrieved from the Internet: <URL:http://www.lycomato.com/> 'retrieved on 2003-03-05! ---	1-27
T	HEALTY ORIGINS-LYC-O-MATO CLINICAL TRIO LYCOPENE, 60 SOFTGELS , 'Online! XP002233575 Retrieved from the Internet: <URL:http://www.lifesvigor.com/products/378105.html> 'retrieved on 2003-03-05! ---	1-27
P,X	WO 02 058683 A (LYCORED NATURAL PRODUCTS INDUSTRIES ET AL-.) 1 August 2002 (2002-08-01) page 6, line 20 - line 23; claims 28,31,38,39 ---	12-19, 22-27
Y	W. STAHL ET AL.: "Dietary Tomato Paste Protects against Ultraviolet Light Induced Erythema in Humans" JOURNAL OF NUTRITION, vol. 131, 2001, pages 1449-1451, XP002233576 cited in the application page 1450, right-hand column -page 1451, left-hand column ---	1-11
Y	WO 00 13654 A (ISRAELI BIOTECHNOLOGY RESEARCH) 16 March 2000 (2000-03-16) page 1 -page 4, line 21; claim 1 ---	1-11
A	US 5 290 605 A (SHAPIRA NIVA) 1 March 1994 (1994-03-01) cited in the application claims ---	1-11
A	US 6 110 478 A (HARANG BENOIT) 29 August 2000 (2000-08-29) cited in the application claims -----	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intel bnal application No.
PCT/IL 02/00875

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1 - 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

ation on patent family members

Internat Application No
PCT/IL 02/00875

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02058683 A	01-08-2002	WO 02058683 A2	01-08-2002
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